REMARKS

Reconsideration and withdrawal of the rejections of the pending claims is respectively requested, in view of the provided amendments and the following remarks. Claims 1-26 are pending. Claims 8, 20 and 22-26 have been withdrawn by the Examiner as directed to non-elected subject matter.

AMENDMENTS TO THE CLAIMS

The claims are amended to address informalities and to address points raised by the Examiner. Thus, claim 1 is amended to correctly indicate a subscript for "r'" in the second element of the Markush group defining L_3. This conforms to usage in the other elements of that Markush group. A comma is also added. The definition for r' remains unchanged, and the amendment is offered simply for clarity. An open parenthesis is added to the third element of the Markush group defining L_3, as suggested by the Examiner. Claim 2 is amended for greater clarity by removing certain elements of the Markush group, without prejudice.

Claim 11 is amended for greater clarity by removing a definition for integer q. Claim 12 is also amended for greater clarity by copying the integer definitions of claim 11 to that claim. This is fully supported by the specification, e.g., pages 21-23, where the integer definitions are submitted to be applied to all of the formulas taught on those pages.

ELECTION AND RESTRICTIONS

At page 2 of the Office Action, the Examiner has now withdrawn claim 8 from consideration on the grounds that SEQ ID NO: 3 represents non-elected subject matter. Applicants respectfully remind the Examiner that a species election requirement was imposed as to the sequences. A species election requirement is made for examination purposes. If the subject matter of claims 1-7 is found to be free of the cited art, it is respectfully urged that claim 8 be rejoined.

THE SPECIFICATION DOES NOT CONTAIN NEW MATTER

At page 2 of the Office Action, the Examiner has alleged that the correction of several nucleotide phosphate groups at pages 11 and 12 of the specification constitutes impermissible new matter. The Examiner stated that, "[a]pplicants assert this change does not introduce new matter because the use of X in these structures was an informality that would be readily recognized by the ordinary artisan. This is not persuasive because there is no evidence or reasoning presented

describing why one would make the assumption that positions designated as X were meant to be M and were not intended to define a substituent distinct from M."

Applicants respectfully disagree. Applicants are permitted to correct an obvious error in the description of a patent application by simply conforming the erroneous description to another part of the specification. According to the Manual of Patent Examining Procedure ("MPEP") (version 8, Rev. 5, page 2100-168), "[a]n amendment to correct an obvious error does not constitute new matter where one skilled in the art would not only recognize the existence of the error in the specification, but also recognize the appropriate correction. *In re Oda*, 443 F.2d 1200, 170 USPQ 268 (CCPA 1971)."

In the present application, the nucleotide compounds are generally shown on pages 12-13 with phosphate groups. The illustrated phosphate groups are drawn with either S=, X=, or M= moieties. M is defined as being either O or S. The Examiner has taken the position that "X" is not defined by the specification in this context. The only other variable in analogous structural locations is M. Another possible choice offered by the remaining structures for correcting this obvious error would be to replace X with S. However, there would be no reason to correct X by substituting S, since S is an element, and not a variable. For this reason, it is respectfully submitted that the ordinary artisan would readily recognize (in view of the structure of the formulas at pages 11 and 12) that: (a) if the variable X lacks a definition and (b) he would then readily recognize that the only other variable given is "M" and that variable M is interchangeable with variable X, thus meeting the legal requirement for a correction that does not represent new matter.

Further still, the Examiner's attention is respectfully directed to the examples and figures provided as part of the instant patent application. For instance, Fig. 5 illustrates AS1 and AS2 oligonucleotides that each have a phosphororothioate backbone, and Fig. 2 illustrates an oligonucleotide that has a phosphorodiester backbone, thus confirming that the scope of "M" is simply that which is exemplified by the provided examples and figures of the patent application.

For all of these reasons, reconsideration and withdrawal of this ground of objection to the specification is respectfully requested.

THE OBJECTIONS TO THE CLAIMS ARE OBVIATED

The Examiner has objected to claim 3 for an extraneous "is". The provided amendment to claim 3 is submitted to obviate this ground of objection.

The Examiner has objected to claim 10 as allegedly repetitive, on the grounds that the

descriptions of formulas (i) to (iv) does not define a direction for reading the subject nucleotide or oligonucleotide molecules of X_2 and/or X_3. The Examiner's attention to this point is appreciated, and the previously provided explanation is clarified, as follows. The description of, e.g., "bis" is intended to convey that the polymer comprises as many as two branches. The description of, e.g., "bis 3' " is intended to convey that each polymer comprises as many as two branches, each with a respective set of linkers, and each with an oligonucleotide, wherein the 3' amino-terminus of the oligonucleotide is adjacent to the linkers and therefore proximal to (on the side of) the polymer (R_1, R_2, R_3). "Bis 3', 5' " is intended to convey that the 3' amino-terminus of the first polymer is proximal to the polymer, and that the 5' amino-terminus of the second oligonucleotide is proximal to the polymer, and so forth.

This can be readily appreciated by considering the provided examples and figures. The structures on pages 42-43 illustrate the terminal modification of the phosphate groups for bonding between the polymer and the oligonulceotides. This is clearly either 3'- or 5'-, as annoted on the provided structures.

The Examiner has objected to claim 1 for lacking an open parenthesis in the definition of L_3 and to claim 1 for allegedly lacking a period. The provided amendments to claims 1 and 2, above, are submitted to obviate these grounds of objection.

REJECTIONS UNDER 35 U.S.C. 112, SECOND PARAGRAPH ARE ADDRESSED OR OBVIATED

At page 4 of the Office Action, claims 2, 4 and 8 are rejected under 35 U.S.C. 112, second paragraph, as allegedly indefinite.

The Examiner has rejected claim 2 because the duplex structure is allegedly unclear. Applicants respectfully disagree. Claim 1, as amended, now makes it clear that, "X_1 is a single or double stranded oligonucleotide residue wherein the oligonucleotide ranges in size from 10 to 1,000 nucleotides..." Claim 2 is now amended to redact the noted duplex structure as redundant to the recitation of claim 1 requiring that X_1 is single or double stranded.

The Examiner has rejected claim 4 for an allegedly insufficient antecedent basis for M in claim 1. Claim 4 is now amended to depend from claim 2, thus obviating this ground of rejection.

The Examiner has rejected claim 8 on the grounds that, "any compatible nucleotide" lacks clarity. The Examiner has withdrawn claim 8 from prosecution (see above). Thus, this ground of rejection is urged to be moot. However, if the Examiner rejoins claim 8 to the claims under

prosecution, Applicants will amend that claim to remove the "any compatible nucleotide" phrase, in order to obviate this ground of rejection. The Examiner is alternatively authorized to remove the phrase "any compatible nucleotide" by Examiner's amendment, if doing so will place the claims into condition for allowance.

Thus, for all of the reasons provided above, reconsideration and withdrawal of all grounds of rejection under 35 U.S.C. 112, second paragraph, is respectfully requested.

THE CLAIMS ARE ENABLED UNDER 35 U.S.C. 112, FIRST PARAGRAPH

At page 6 of the Office Action, claim 2 is rejected under 35 U.S.C. 112, first paragraph, as allegedly failing to comply with the written description requirement for the correction of an obvious error in changing "X" to "M" as a variable linked to phosphate groups. This point has been discussed above in response to the objection to the specification on the same basis.

It is respectfully urged that amended claim 2 does not contain new matter, since the correction of X to M would have been recognized as the correction of an obvious error. The Examiner has taken the position that there is no definition of X that is pertinent to the context of claim 2. Nevertheless, M is the variable that is present in adjacent structures and that is defined by the specification. As also noted above, the exemplified compounds, as illustrated by the figures, describe backbones of either S or O, independently selected, thus confirming that the corrected structures are fully in conformity with the examples as provided.

For all of the above reasons, reconsideration and withdrawal of the rejection under 35 U.S.C. 112, first paragraph is respectfully requested.

THE CLAIMS ARE NONOBVIOUS UNDER 35 U.S.C. 103(a)

At page 6 of the Office Action, the previous rejection of claims 1-3, 5-19 and 21 is maintained. Thus, these claims are rejected under 35 U.S.C. 103(a) as allegedly unpatentable over Teng et al. ("Teng;" US 6,887,906) in view of Greenwald et al. ("Greenwald;" US 6,303,569) and Dandliker et al. ("Dandliker;" US 5,707,813).

The Examiner states that Teng teaches compositions of antisense oligonucleotides useful for therapeutic purposes. One of these is stated to be targeted to bcl-2 and identical to instant SEQ ID NO: 1. The Examiner further states that, Teng also teach that the antisense compounds can comprise modified linkages such as phosphorothioates, and can be provided in prodrug form.

The Examiner concedes that Teng does not explicitly teach the use of polymeric prodrugs. The Examiner points to Greenwald as teaching that poor solubility and rapid degradation *in vivo* are problems remedied by employing polymeric prodrugs.

> At page 7 of the Office Action, the Examiner points to Greenwald for the proposition that, poor solubility and rapid degradation *in* vivo are recognized problems of some therapeutic agents. One solution to these problems is the use of prodrugs; inactive forms of a drug that are metabolized within the body to form the active agent. The use of prodrugs can allow one to increase the solubility and lifetime of a drug.

The Examiner concludes that, "It would have been obvious to one of ordinary skill in the art at the time of invention to produce the bcl-2 sequence of Teng et al. in prodrug form as a polymeric prodrug, including a polymeric bis-prodrug, as taught by Greenwald et al."

The Examiner then turns to Dandliker for the proposition "[i]t is further obvious to use hexylamine linkers as a component of the prodrug because Dandliker et al. teach that the person of ordinary skill in the art would be familiar with the use of such linkers due to the commercial availability of reagents that make such linkers and the extensive use of hexylamine linkers for producing a variety of oligonucleotide conjugates."

Applicants respectfully traverse. Referring to claim 1, the compound has L_2 and L_3 as independently selected spacing groups, as specified. L_2 and L_3 range in size from about 2 to about 10 carbons, and are interposed between the oligonucleotide and the releasable linking moieties of L_1 and L_4. The invention of claim 1 solves a long-standing and unmet need for an optimal polymer oligonucleotide conjugate. It is respectfully requested that the Examiner take administrative notice that chemistry, and particularly the chemistry of nucleotides, is an unpredictable art area. Certainly, none of the art of record, taken separately or in any combination, teaches or demonstrates an actual polymer oligonucleotide conjugate that meets the limitations of claim 1.

The Supreme Court recently explained that "a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007). The Court further opined that, "[I]t can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does." While *KSR* held that the motivation to combine need not only come from the cited references, it is submitted that post *KSR*, the Patent Office is still required to articulate some technical reason or reasons why the artisan would have thought to make the alleged combination.

As explained by Teng, the problem solved by their compounds is, to provide, "compositions and methods which enhance the transport of nucleic acids, especially oligonucleotides at various sites in the alimentary canal of an animal..." (Abstract). As conceded by the Examiner at page 7 of the Office Action, "Teng et al. do not explicitly teach the use of polymeric prodrugs." It is respectfully submitted that this is not a minor deficiency, that can be readily overlooked in sustaining a *prima facie* obviousness rejection. Without a teaching in the art about the nature of the linkage between a polymer and an oligonucleotide to provide a prodrug, *i.e.* a form that is stable *in vitro* and releasable *in vivo*, the ordinary artisan would have had no reasonable expectation of success in making and using any of the claimed compounds.

The Examiner relies upon Greenwald to remedy the clear deficiency of Teng, for the proposition that polymers, such as polyalkylene oxides, can be linked to drugs of interest to obtain improved kinetics and/or useful prodrugs. Greenwald speaks generally of nucleic acids at Col. 19, last paragraph, explaining that, "[t]his includes amino acid sequences, nucleic acids (DNA, RNA), peptide nucleic acids (PNA), antibody fragments, single chain binding proteins...." However, it is submitted that nowhere does Greenwald remedy the clear deficiency of Teng in not teaching or suggesting the specific conjugate as claimed. In particular, Greenwald fails to teach or suggest providing an amino-linked separator or tail between the oligonucleotide and the polymer as required by claim 1.

Dandliker is offered to remedy the above-described deficiency. However, it is respectfully submitted that Dandliker is non-analogous art and inappropriate to be cited for the present alleged rejection. Dandliker teaches an oligonucleotide linked to a detectably labeled marker component comprising a fluorophore moiety. In addition, Dandliker does not teach that the marker moiety is releasable from the oligonucleotide. For all of these reasons, it is submitted that Dandliker is non-analogous to the invention as claimed, because tagged oligonucleotides are not prodrugs, and are submitted to be completely unrelated in a functional and in a structural way, to a polymer-conjugated oligonucleotide.

Even assuming, *arguendo*, that Dandliker is accepted as analogous art, the Patent Office has still failed to meet its legal burden of sustaining a *prima facie* rejection. Among the myriad of possible structures for a polymer-conjugated oligonucleotide, there is no reason made of record as to why the artisan would have looked to any of Teng, Greenwald and Dandliker to pick elements to teach the specific structure as claimed. For example, the ordinary artisan, who has looked to Greenwald, would have more likely conjugated the releasable linker directly to a nucleic acid base,

instead of via an additional linker. Figure 12 of Greenwald illustrates PEG conjugated on the amine of the nucleoside. This can only suggest that a polymer should be conjugated via the nucleic acid base. It fails to teach or suggest utilizing the "tail" structure as recited by the pending claims.

At best, this amounts to an "obvious to try" or a hindsight reconstruction. While there is not an absolute prohibition on obvious to try or hindsight reconstruction, on the facts of the presently pending claims, given the state of the art at the time the instant patent application was filed, it is submitted that there would have been no guidance in the art of record, in the state of the art, or the "common sense" noted by the Court in *KSR*, pointing the artisan to the specific structure of claim 1, et seq. To the contrary, it is urged that common sense would have led the artisan to try to directly react the oligonucleotide to the polymer via a releasable linker, without adding the potential complexity of an additional linker.

This clear deficiency is submitted to negate any alleged *prima facie* obviousness. If the Examiner has personal information that would remedy this clear deficiency, she is respectfully requested to make such information of record in a Declaration under 37 CFR 1.132.

Absent such a showing, it is respectfully urged that this ground of rejection be reconsidered and withdrawn.

FEES

This response is being with a Petition for Extension of Time for one month, pursuant to 37 CFR 1.136(a), and a Request for Continued Examination, together with the required fees. Thus, no further fees are believed to be required. If, on the other hand, it is determined that any further fees are due or any overpayment has been made, the Assistant Commissioner is hereby authorized to debit or credit such sum to Deposit Account No. 02-2275.

Pursuant to 37 C.F.R. 1.136(a)(3), please treat this and any concurrent or future reply in this application that requires a petition for an extension of time for its timely submission as incorporating a petition for extension of time for the appropriate length of time. The fee associated therewith is to be charged to Deposit Account No. 02-2275.

An early and favorable action on the merits is earnestly solicited.

Respectfully submitted,

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CERTIFICATE
I hereby certify that this correspondence is being EFS-Web or facsimile transmitted to the USPTO or deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: the Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on September 24, 2007.
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